In This Issue . . .

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Collagen Defect Found In A Severe Form of Epidermolysis Bullosa

A variety of evidence has suggested that the hereditary forms of epidermolysis bullosa (EB) are caused by defective anchoring fibrils. Researchers have generally found that these fibrils, which are located between the dermis and epidermis and help to hold the two skin layers together, are absent, reduced in number, or otherwise abnormal in the skin of patients with hereditary EB.

In this issue, Leena Bruckner-Tuderman, Yoshihiko Mitsuhashi, Urs Schnyder, and Peter Bruckner of the University Hospital and the Swiss Federal Institute of Technology in Zurich report that the anchoring fibrils are missing in at least some patients with hereditary EB because the patients' skin lacks type VII collagen, the principal protein component of the fibrils. Bruckner-Tuderman stresses, however, that this finding may apply only to patients with the mutilating form of severe generalized recessive dystrophic EB (SGRDEB).

The Zurich workers examined skin samples from four patients with mutilating SGRDEB and from normal controls. They found that type VII collagen was readily detectable in the control skin, but not in the patients' samples. "We have shown that we can't find type VII collagen in the skin of these patients by several methods. The absence of the anchoring fibrils is the result of the absence of type VII collagen," Bruckner-Tuderman concludes.

The researchers have not yet identified the defect in SGRDEB skin that causes the type VII collagen deficiency. The problem could be at any stage in the synthesis or assembly of the collagen molecule, or the protein might be made, but rapidly broken down by collagenase enzymes.

In the past, there have been discrepancies in researchers' findings concerning the anchoring fibrils and type VII collagen content of skin from patients with recessive dystrophic EB. In some cases no anchoring fibrils or type VII collagen have been found, whereas in others the materials have been present. Recessive dystrophic EB is apparently a heterogeneous disease with different manifestations that may be caused by diverse genetic defects. For this reason, the Zurich workers note that the different subgroups of patients may not be comparable. However, the absence of type VII collagen may be characteristic of the subgroup with the most severe form of dystrophic EB, and may be useful for doing prenatal diagnosis of the condition in families known to be affected by the disease.

Keratinocytes in Culture Show Lipid Changes Similar to Those in Skin

As keratinocytes move from the living layer of the epidermis of the skin into the stratum corneum, the composition of the lipids they make changes dramatically. Until recently, those changes could not be studied readily. "It's been difficult to look at lipid metabolism because the cultures weren't adequate," says Kathi Madison of the University of Iowa College of Medicine in Iowa City.

In this issue, however, Madison and her Iowa colleagues Donald Swartzendruber, Philip Wertz and Donald Downing report that a new culture system that they have developed gives much improved results when it comes to studying lipid metabolism during keratinocyte differentiation. "We showed that the composition changes in lipids that accompany differentiation were reproduced in these cultures," Madison says.

In the culture system devised by the Iowa workers, keratinocytes are grown over a layer of mouse dermis in such a way that the keratinocytes are at the interface between the liquid culture medium and the air (see Madison et al, *J Invest Dermatol* 90:110, 1988). When cultured this way, the cells undergo morphological changes much like those seen in the keratinocytes of the skin as they move up from the bottom layer of the epidermis into the stratum corneum.

In the skin, the living layer of the epidermis is rich in the phospholipids and glucosyl ceramides. In contrast, the stratum corneum contains little of these lipids, but has, instead, a high proportion of the linoleic acid-containing ceramides and free fatty acids. As the cultured cells become cornified, they shift their pattern of lipid synthesis, the Iowa workers now find, so that it becomes more like that seen in the stratum corneum. Keratinocytes grown the old way, on plastic and submerged in the culture fluid, do not show this shift but continue to produce a lipid pattern more like that of the less-differentiated cells of the living epidermal layer.

The way is now open, Madison says, to study the pathways of lipid metabolism and their control in keratinocytes differentiating in culture. This will help in understanding not only the normal formation of the lipid layer of the stratum corneum, which is the body's main barrier to water loss, but also the abnormalities in lipid metabolism that may occur in disease states such as essential fatty acid deficiency and recessive X-linked ichthyosis.

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Gamma-Interferon Inhibits Wound Healing and Inflammation in Mice

The lymphokines, the molecules by which the cells of the immune system communicate with one another, have also been implicated as regulators of inflammation and wound healing, at least in in vitro systems. In this issue, Richard Granstein, Mary Rose Deak, Steven Jacques, Randall Margolis, Thomas Flote, Diana Whitaker, Frederick Long, and Edward Amento of Massachusetts General Hospital and Harvard Medical School in Boston now report that the lymphokine gamma-interferon inhibits wound healing when administered systemically to mice. Its systemic effects were not completely as predicted by the in vitro results, however.

To study the in vivo effects of gamma-interferon on wound healing, Granstein and his colleagues used a laser to wound the skin of anesthetized mice. The researchers found that the time required for the damaged skin to heal was about 25% longer in animals that were treated with gamma-interferon, which was administered either subcutaneously or intraperitoneally. The wounds of the treated animals contained less collagen than those of controls. "You can reduce collagen synthesis at a distant site with gamma-interferon," Granstein says.

This result is consistent with previous findings in which researchers, including members of the Harvard group, had shown that the lymphokine inhibits collagen synthesis by cells growing in culture. The reduced synthesis in vitro, and possibly in vivo as well, is the result of decreased expression of the collagen genes.

The Harvard workers found, however, that gamma-interferon administration reduced the inflammatory changes in the healing wounds. It also inhibited the responses to known inflammatory agents, including interleukin 1. "The inflammation results were a real surprise," Granstein remarks. "Based on in vitro studies, one would have predicted that gamma-interferon would have increased inflammation." For example, the in vitro work indicated that the lymphokine attracts white blood cells, yet the damaged skin of the treated animals contained fewer inflammatory cells than that of the control animals. The mechanism of the anti-inflammatory action of gamma-interferon in vivo is not yet known.

The information being gleaned in these studies may have clinical significance, Granstein says. It may be possible to use gamma-interferon to prevent the abnormal collagen accumulation that occurs in keloid scars or in diseases such as scleroderma. The agent may also have potential as an anti-inflammatory agent.